

Review Article**HYDROGEL: AN UPDATED PRIMER****LALITA DEVI*, PUNAM GABA****Department of Pharmaceutics, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial, College of Pharmacy, Bela (Ropar)**
Email: pharmacistlalita@gmail.com*Received: 28 Mar 2019 Revised and Accepted: 29 Jun 2019***ABSTRACT**

Hydrogels are broadly utilized as of late because of their numerous profitable properties, for example, more water content, greater adaptability, versatility and biocompatibility. Hydrogels are the 3-Dimensional polymeric system structure of hydrophilic polymers which are the center around medication that is discharged in a controlled way. A few medications have low bioavailability hydrogel is used to upgrade the bioavailability of a medication. Hydrogels play an imperative job in tissue designing (transplant cells, ligament, bone and smooth muscle) controlled medication conveyance framework and regenerative drugs, contact lens due to greater biodegradability and biocompatibility. The essential objective of hydrogels is the medication is discharged in a controlled rate and maximum therapeutic effects, limit unfavorable impacts and better patient consistency. The fundamental point of this survey concentrated on the late progression of hydrogel attributes and biomedical applications.

Keywords: Hydrogel, Cross-linking, Drug delivery, Wound dressings

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INTRODUCTION

Hydrogels are 3D (three dimensional), cross-connected systems of water solvent polymers (hydrophilic polymers). Huge pore size and water content in the hydrogel to enhance the medication discharge for a few days [1]. They have the characteristics to absorb a considerable amount of water and swell without dissolving. The hydrogel is a novel transporter for particular or Novel Drug Delivery System (NDDS). To accomplish a controlled rate of a medication, an active pharmaceutical ingredient is incorporated into a polymeric system structure in this manner the medication is discharged in a controlled rate. Various types of the natural and synthetic polymer have been utilized as medication transporters. In synthetic polymers which are man-made polymers that contain a few synthetic chemical moieties that are connected or different cross connecting agents, collagen which is gotten from animals may contain remaining development and infections of animal tissues which are cause some ominous impacts to people. Characteristic polymers are broadly utilized in hydrogel since they normally happen, unadulterated and promptly accessible, non-harmful and biodegradable [2-5]. Sodium alginate based layout hydrogels are incorporated by utilizing diverse sorts of monomers, for example, acrylamide, methacrylamide and N-isopropyl acrylamide for controlled medication discharge. Synthetic polymers are also utilized in the preparation of hydrogel-like poly (hydroxyl ethyl methacrylate), polyethylene glycol, polyamides, poly (acrylic acid). Hydrogel innovations are applied in sterile items, sealing, novel drug delivery system, biomedical reason tissue building, regenerative medicine, diagnostics, proteins and peptides and medication conveyance in malignancy or targeting therapy. In therapeutic and pharmaceutical field hydrogels are the various applications [6-8]. Hydrogels resemble regular living tissue as a contrast with alternate kinds of engineered biomaterials. Because of their more water content and simple to form this is close to common tissue [6]. The primary aim to build up the medication conveyance frameworks is to protect an active therapeutic molecule from premature degradation, improve drug efficacy and reduce unwanted effects. Controlled discharge frameworks can meet the criteria by keeping the medication concentration within the therapeutic window over an extended period of time, limiting dose and recurrence of administration [9, 10]. Stimuli-responsive hydrogel frameworks have been essentially considered for therapeutic delivery applications as they respond to changes in natural conditions. The diversity of materials and particular natural and physicochemical attributes demonstrate a variety of potential for pharmaceutical applications. To

enhance the stability of sensitive macromolecules like proteins, antibodies or nucleic acid are loaded in the hydrogel system. Mostly, hydrogels with "smart" behaviors undergo reversible shape deformations in response to outermost stimuli like heat, electricity or light. Currently, two of the most popular "smart" hydrogels like hydrogel actuators (HAs) and shape memory hydrogels (SMHs) have attracted increasing due to their promising probable applications in biomedicine and soft robotics and as artificial muscles. Besides, various approaches for manufacturing smart hydrogels with inhomogeneous formation and fabrication technologies support in hydrogel-based actuators. Yet there is still a long way to go in making complex deformations from 2D to 3D, just like general and collaborative multi-step actuation in natural life, partly due to chemical structures delicate to multi stimuli should be combined in a hydrogel matrix to achieve multi-step actuation imitating natural life. Intrinsic interest on advanced and different chemical approaches and their outer stimulation should be investigated more. In the future trends of "smart" hydrogels are to develop the multi-stimulative hydrogels with complex but programmed self-folding, twisting and bending performance by designing inhomogeneous hydrogels through the formation of enhanced fabrication technologies [11].

Properties of hydrogels**(a) Swelling properties**

Cross connecting operators assume an imperative job in hydrogel formation. It is a variable that impacts on the assimilation of water. A little change in atmosphere condition impact on a hydrogel it might be quick and reversible changes in a hydrogel. pH, temperature, electric signal, nearness of chemical or other ionic species are the atmosphere parameters that impact on a physical effect on the hydrogel. These progressions may happen at the naturally visible level as the precipitate from the progressions happens in size and water content in hydrogel formation [12]. The measure of fluid medication medium which can be incorporated in a hydrogel can be computed by the gravimetric technique and the proportion which can be demonstrated as a swelling proportion.

$$\text{Swelling Ratio} = \frac{\text{Weight of hydrogel in swollen states} - \text{Weight of a hydrogel in dry state}}{\text{Weight of hydrogel}}$$

Hydrogels contain acidic or basic functional atoms respond to change in the outer condition pH. The level of ionization of the functional groups dictates its swelling profile and subsequently the volume changes [13].

(b) Mechanical properties

Mechanical properties of the hydrogel are critical pretend in the pharmaceutical and biomedical perspective. The assessment of the mechanical property is an imperative parameter in various biomedical reasons like tendon and ligament repair, wound dressing material, lattice for medication conveyance, tissue designing and as ligament substitution material. The hydrogel ought to be with the end goal that it can support the physical surface required amid the conveyance of time at a predetermined rate. By altering the measure of cross connecting for the coveted mechanical property of the hydrogel can be acquired. If we raise the concentration of the cross-connecting agent in the hydrogel the stronger can be formed but it is inversely proportional to the percent elongation of the hydrogel, as a result, the brittle hydrogel is formed. By changing the level of cross-connecting agents to accomplish the desired mechanical property of hydrogel [12].

(c) Biocompatible properties

It is basic for the hydrogels to be biocompatible and nonpoisonous in order to make it relevant in the biomedical field. Biocompatibility is the capacity of a material to work with a suitable host reaction in particular demands [13]. Biocompatibility is the capacity of a material to perform with a proper host reaction in a particular application. Biocompatibility comprises fundamentally of two components:

- Biofunctionality i.e. the capacity of a material to play out the particular undertaking for which it is expected.
- Bio-security i.e. fitting host reaction foundational as well as locally (the encompassing tissue), the nonappearance of mutagenesis, cytotoxicity, or potentially carcinogenesis [14].

(d) Porosity and permeation

The procedure of stage partition throughout union pores might be shaped in hydrogels or they may present as littler pores inside the system. The fundamental variables of hydrogels matrix are normal pore estimate, the pore measure dispersion and the pore interconnections, these components are frequently testing to process and are for the most part included together in the parameter called tortuosity. The pore-measure appropriations of hydrogels are viably affected by the following three components:

- 1) The concentration of the chemical cross-connections of the polymer strands and its concentration determined by the underlying proportion of cross-linker to monomer.
- 2) Grouping of the physical entanglements of the polymer strands and is additionally associated with the concentration of beginning atoms present inside the hydrogel.
- 3) The net charge of the polyelectrolyte hydrogel as well as it is also dependent on the initial concentration of cationic or anionic nature.

Count of the elements by utilizing the arrangement of hydrogel with nominal concentrations of monomer and cross-linker:

$$\%T = \text{weight of monomer} + \text{weight of x-crosslinker} / \text{add up to volume}$$

$$\%C = \text{weight of x-crosslinker} / \text{weight of monomer} + \text{weight of x-crosslinker}$$

Above all else, porosity can be calculated by theoretic strategies, similar to unit shape investigation, mass procedure, and fluid displacement technique. These assessments are integrated by optical and electronic microscopy. More convenient strategies are the mercury porosimetry dependent on Washburn's condition, gas pycnometry, gas adsorption, fluid expulsion porosity, an examine that permits assessing test's penetrability as well, fine stream porosity. Additionally, a substitute measure is the Micro-CT, likewise called X-beam microtomography, a relatively new imaging innovation, clearly communicated as non-ruinous high goals radiography, metal 1 requirements for subjective and additionally quantitative tests on tests and estimation of their pore interconnections. Between the quantitative tests that can be performed, the normal pore measure, pore estimate appropriation, pore interconnection, swaggers/dividers thickness and anisotropy/isotropy of the example (in the feeling of essence/nonappearance of the particular introduction of the pores)

can be dictated by smaller scale CT. It is yet, these days, an expensive method both in terms of cash and time [15]. Microscopy procedures are broadly valuable in various distinctive examines including the hydrogels. They are involved in both qualitative and quantitative studies. Quickly, by microscopy strategies, geology and surface morphology can be evaluated. These methods can be characterized in numerous classifications, by expanding amplification control: optical microscopy, stereo microscopy, scanning electron microscope and transmission electron microscope, atomic force microscopy.

Advantages [16]

- Due to their more water content, they have a level of flexibility fundamentally the same as regular tissue.
- Release of medicines or supplements in a suitable time.
- They are biocompatible, ecological and can be infused.
- Hydrogels likewise have great transport properties and simple to modify.
- Hydrogels are delicate towards the pH changes and also for temperature.
- Reduce side effects.
- Improved patient compliance.
- The drug is targeted at a specific site such as colon targeting.
- Enhanced the bioavailability and half-life of a drug.

Disadvantages

- In the case of ophthalmic preparation like contact lenses cause lens deposition, hypoxia, drying out and eye reactions.
- Can be smart to handle.
- Low mechanical property.
- High cost.
- Difficulty in loading of drugs/nutrients [17, 18]

Hydrogel classification

A. Based on origin

(a) Natural origin

In immature microorganism culture and regulation, natural hydrogels have been customarily utilized because of its profitable properties for example, biocompatibility and biodegradability [21]. Natural origin for example, *kelp*, *dark-colored green growth*, *bacterial culture*, *polysaccharides*, and *proteins* (*collagen*, *gelatin*, and *fibrin*) [22]. The drawback of a natural hydrogel is poor mechanical strength, batch variations are formed.

(b) Synthetic origins

They are artificial polymers, they are idler as a contrast with normal hydrogel to arise from biomaterials. Moreover, synthetic hydrogels have a long time span of usability, more maintenance property and effectively modified [23]. Examples are polyacrylamide, polyethylene glycol, hyaluronic acid. The drawbacks of synthetic origins are the absence of *in vivo* biocompatibility, moderate debasement rates separate into the natural hydrogel.

(c) Hybrid (nanocomposite)

It is a blend of natural and synthetic materials. A blend of structure and association of various particles in a nanocomposite hydrogel can enhance physical, electrical, synthetic and natural properties [24, 25]. Examples are hydroxyapatite nanoparticles polyethylene glycol lattice, tetra hydroxyl PEG acrylate+thiol peptide. The benefit is improved mechanical strength. The disadvantage is undetermined long-term biocompatibility, nanotoxicity or noxious effects are occurring.

B. Based on configuration

In view of their morphology and chemical constitution which are instanced as pursues:

- Amorphous (non-crystalline)
- Semicrystalline: A perplexing mix of undefined and crystalline parts.
- Crystalline.

C. Based on polymeric composition

(a) Homopolymeric hydrogels

It is a polymeric system structure that got from a monomer and cross-linker. A monomer is a fundamental basic unit of a polymer organizes. The cross-connected system structure of homopolymeric hydrogels relies upon a pith of the monomer and polymerization strategy.

(b) Copolymeric hydrogels

It incorporates at least two diverse monomer species with something like one hydrophilic part organized in an arbitrary, square or substituting arrangement along the chain of the polymer organize.

(c) Multipolymer

It is otherwise called interpenetrating polymeric hydrogel (IPN), it is a great class of hydrogels, or in other words, a blend of two autonomous cross-connected polymers (manufactured or potentially natural polymer parts), restricted in a structure (network) development. In semi-interpenetrating polymeric hydrogel incorporates two sections initially is a cross-connected polymer and the second is a noncrosslinked polymer [26].

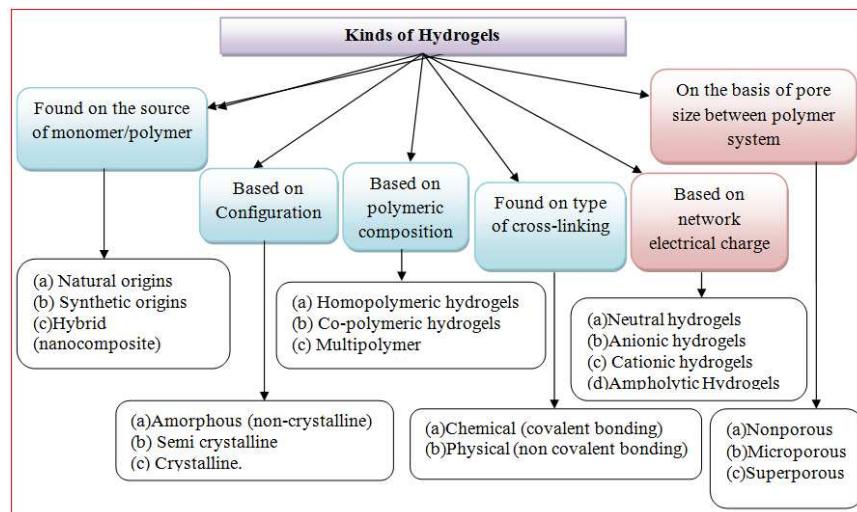


Fig. 1: Classification of hydrogel [16-20]

A. Based on cross-LINKING

It depends on the physical or chemical behavior of the cross-connection intersections. Synthetically cross-connected systems have stable intersections, while physical systems have transitory intersections that outcome from either polymer chain traps or physical collaborations like ionic associations, hydrogen bonds or hydrophobic interactions.

B. Based on network electrical charge

(a) Neutral hydrogels

Neutral hydrogel are also known as nonionic hydrogel. There is no charge on their backbone or side gatherings. Because of water-polymer collaboration, the non-ionic hydrogel swells in fluid medium gradually. Polyacrylamide [27], polyhydroxy ethyl methacrylate [28], polyvinyl alcohol [29], and polyethylene glycol [30], are the precedents of a non-ionic hydrogel.

(b) Anionic hydrogels

Anionic hydrogels have a negative charge. Hydrogel demonstrates more swelling in neutral to basic solution due to dissociation at higher pH. Acrylic acid, p-styrene sulphonic acid, itaconic acid, crotonic acid, maleic acid and methacrylic acid etc [31] are precedents which are utilized in anionic hydrogels.

(c) Cationic hydrogels

Cationic positive charge bearing hydrogels. They show predominant swelling in acidic media since their chain separation is favored at low pH values. Precedents of monomers are utilized in the combination of cationic hydrogels includes vinyl pyridine, aminoethyl methacrylate, diethyl aminoethyl methacrylate and dimethylaminoethyl methacrylate [32, 33].

(d) Ampholytic hydrogels

Ampholytic hydrogels which conveyed negative and additionally positive charges on a similar polymer chain and hold both acidic and essential gatherings in each auxiliary repeating unit. These charges are adjusted at the iso-electric point. A little change in pH can change the general ionic properties of these kinds of hydrogels. Monomers for example N-isopropylacrylamide/[3-(methacryloylamino) propyl dimethyl (3-sulfopropyl) ammonium hydroxide] (NIPAAm/MPSA) are utilized in the synthesis of ampholytic hydrogel.

F. Based on pore size

(a) Nonporous

Diffusion is the mechanism for transport of water swelling in the medium.

(b) Microporous

Microporous hydrogels contain a little pore measure which can be assessed by scanning electron microscope or other microscopic procedure.

(c) Superporous

These hydrogels are incorporated and extensively measured pores; which are gainful in getting uncommonly high swelling rates in a brief timeframe. Such kinds of hydrogels are promising in different methodologies for precedents, superabsorbent, responsive biomedical gadgets and furthermore agriculture etc. Pore size is an important role play in diffusing and correspondingly the swelling rates. Profoundly permeable structures showed quicker and higher swelling [34].

Methods of preparations

Mostly, the thrice essential fragments of hydrogel arrangements included which are monomer, initiator and crosslinker. To direct

the heat of polymerization and the properties of the last hydrogel diluents can be utilized in the formulation, for example, water or different fluid arrangements. Polar monomers are utilized in the planning of hydrogels. As per their beginning materials can be founded on the characteristic polymer, synthetic polymer and mix of the two. The two principle things must be remembered one is the crude material of that item and another is the appropriate strategy to acquire one of a kind and attractive items.

Crude materials

The real materials utilized for combination and planning of PHG are monomers or polymers which can be blended or common polymers for example hydroxyethyl methacrylate, hydroxyl ethoxy ethyl methacrylate, hydroxyl diethoxy ethyl methacrylate, methoxyethyl methacrylate, methoxyethoxyethyl methacrylate, methoxydiethoxyethyl methacrylate, vinyl acetic acid derivation, acrylic acid, ethylene glycol, polyethylene glycol acrylate, polyethylene glycol methacrylate, polyethylene glycol diacrylate, polyethylene glycol dimethacrylate [35], and cross-connecting agents for example epichlorohydrin [36], N,N0-methylene-bisacrylamide [37-39] and divinylsulfone [40]. In a few techniques require initiators, for example, 2, 20-azobis (isobutyronitrile) [41], ammonium persulfate [42] and potassium peroxidisulfate [43].

Polymerization techniques

Solution polymerization or watery polymer solution [44], radiation polymerization [45], or photopolymerization [46, 47], suspension polymerization [48], or inverse suspension polymerization, reversible addition-fragmentation chain transfer polymerization [49] and free radical polymerization [46, 50, 51] are polymerization systems which are utilized to synthesize and prepare hydrogels.

(a) Solution polymerization

The multifunctional cross-connecting agents contain ionic or unbiased monomers which are blended with them (fig. 2). The polymerization is started thermally by UV-irradiation or by a redox initiator framework. The existent of dissolvable is the weighty preferred standpoint of the arrangement polymerization over the bulk polymerization strategy to fill in as a warmth sink. The prepared polymer hydrogels (PHGs) incorporate some unreacted monomers, oligomers, cross-connecting agents, initiator, solvent, extractable polymers and different polluting influences, which are washed with refined water. The phase partition rises of heterogeneous PHGs are started when the measure of water amid polymerization is more than the water content relating to the equilibrium swelling. Typical solvents water, ethanol, water-ethanol blends and benzyl liquor utilized for arrangement polymerization of hydrogels are included. This strategy has been utilized to get ready assortments of hydrogels in the last decades [52, 53].

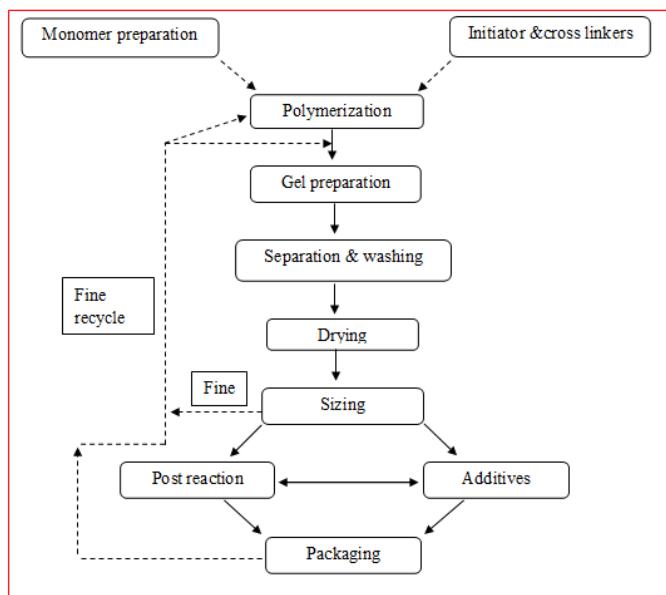


Fig. 2: Solution polymerization technique [52, 53]

(b) Suspension polymerization

Dispersion polymerization is a convenience strategy since the items are gained as powder or microspheres and along these lines crushing is not required. Since the water-in-oil (W/O) process is chosen in inclination to the more typical oil-in-water (O/W), the polymerization is indicated as "backward suspension". In this strategy, the monomers and initiator are circulated in the hydrocarbon stage as a homogenous blend (fig. 3). The

shape and size of particles rely on the consistency of the monomer arrangement, agitation speed, rotor structure and dispersant kind [54]. A few polymer hydrogels smaller scale particles of poly (hydroxyl ethyl methacrylate) have been figured by this technique.

Latterly, polyacrylamide gel is set up by inverse suspension because of its simple evacuation and administration of the risky leftover acrylamide monomer from the polymer [55].

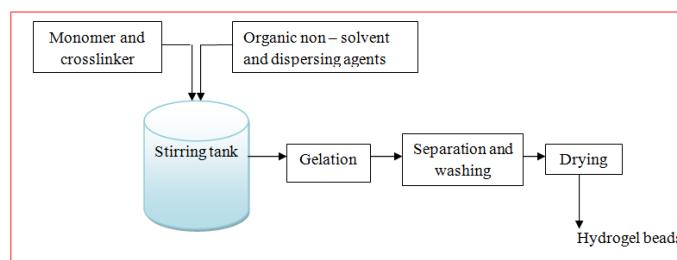


Fig. 3: Suspension polymerization [54]

(c) Polymerization by irradiation

Ionizing high vitality radiation (gamma and electron beams) has been utilized to start the polymerization for the planning of the PHGs of unsaturated mixes. Polymer chains are formed because of illumination fluid polymer arrangement. Hydroxyl radicals are framed because of radiolysis of water particle which ultimately attacks the polymer chain forming macroradicals. Recombination of the macroradicals on various chains activated to the framing of covalent bonds lastly a cross-connected structure. Precedents of cross-connected polymers are poly (vinyl liquor), poly (ethylene glycol) and poly (acrylic acid). The radiation initiation has valuable over chemical initiation is the development of pure and initiator free hydrogel [45, 56-58].

(d) Bulk polymerization

Vinyl monomers have a tendency to form hydrogels. To produce in bulk numerous kinds of monomers can be utilized and a little amount of cross-connecting specialist is added to make the hydrogel formulation. Radiation, ultraviolet or chemical catalysts which are the initiators utilized in polymerization response and the decisions of an appropriate initiator rely upon the kind of monomers and solvents being utilized. Polymerized hydrogels are different structures for example films and layers, poles, particles and emulsions. This strategy is the least difficult, which contained just monomer and monomer, solvent initiators. The thickness of response increments notably with the change which creates the warmth amid polymerization. These complications can be maintained a strategic distance from by controlling the response. The bulk polymerization of monomers to make a homogeneous hydrogel creating a polished, straightforward polymer grid which is hard. At the point when putting in water, the shiny network swells to end up delicate and flexible [59].

(e) Grafting to a support

Conventionally, hydrogels arranged by bulk polymerization method have an innate powerless structure. To improve the mechanical properties of a hydrogel, it tends to be joined on the surface covered onto stronger support. In this strategy includes the initiations of free radicals onto a stronger support surface and afterward polymerizing monomers specifically onto it. As a result, a sequence of monomers is covalently attached to the support [59].

Applications of hydrogels

A various methodologies have been proposed to accomplish medicate conveyance frameworks for sufficient treatment. Among them, hydrogels are one which has astounding biocompatibility to accomplish controlled discharge gadgets, bioadhesive gadgets or targetable gadgets of remedial operators. Hydrogel-based medication conveyance gadgets can be utilized as orally, rectally, visually, epidermally and subcutaneous application.

Peroral medication delivery

Drug conveyance oral route is the most normal regular course in the pharmaceutical area. Mouth, stomach, small digestive system and colon are the fundamental sites that can convey the hydrogel. Due to their swelling trademark or bioadhesive attributes within the sight of a biological fluid, hydrogels can be a valuable gadget for discharging drugs in a controlled way at these coveted sites. They can likewise hold fast to certain particular locales in the oral route, which results in expanded medication focus and improving the medication ingestion at the site of activity.

Wound recuperating

The ligament contains a changed polysaccharide that has been utilized in the arrangement of hydrogels to fix ligament surrenders have been developed [60]. The polysaccharide is functionalized with methacrylate and aldehyde gather which respond with proteins of skin tissues, while the methacrylate cross connections with the spine of disaccharide chondroitin hence a system is framed from where the chondrocytes cells are rescue [61]. In wound-mending treatment, poly (hydroxyethyl methacrylate) based hydrogels are utilized for consuming dressings applications. Honey hydrogels have been utilized for provoking wound mending. Honey is utilized as a

cross-connecting operator in the hydrogel network most adequate, effectively peeled and straight forward system [62]. The hydrogel of gelatin and polyvinyl alcohol along with blood coagulants have been figured. The cell adhesive hydrogel guaranteed preferred impact over relating gel or balm in controlling blood coagulation [63]. In the treatment of grinding cavity wounds, hydrogel dressing is broadly used [64]. Amorphous gels are by and large reapplied consistently while sheet hydrogels are normally changed 2-3 times a week [65] granugelR (convatec), purilongelR (coloplast), woundtabR (first water) are marketed products which are used in wound dressings. The most broadly utilized characteristic polymers are cellulose, chitin, chitosan and gelatin utilized in regenerative prescription, implantable matter, frameworks for tissue building or controlled discharge carriers [66]. Chitosan is utilized in wound dressings as a result of its diminished injury recuperating times and enhanced tissue organization [67]. In regenerative drugs for cell conveyance and dressing material or wounds, microporous hydrogels are utilized in regenerative drugs for cell conveyance and dressing matter [68, 69].

Rectal delivery

The rectal route has been utilized to convey numerous kinds of medications, while quiet worthiness is variable because of the inconvenience emerging from managed dose frames. It's essential applications have been for neighborhood treatment of ailments related to the rectum, similar to hemorrhoids. Furthermore, it is notable that medications consumed from the lower some portion of the rectum deplete into the foundational route specifically. Therefore, the rectal route is a valuable organization route for those medications which achieves the first-pass metabolism. Traditional suppositories have hindered that medication diffuse out of suppositories unplanned way in the rectum and some of the times relocate upwards to the colon. This frequently prompts a variety of the bioavailability of specific medications specifically, for medications that experience broad first-pass end. Therefore hydrogel has a greater advantage over conventional suppository [70].

Proteins and peptides delivery

For a few medications like NSAIDs (non-steroidal anti-inflammatory drugs) or large atoms as proteins and peptides, hydrogels offer more advantageous, good and stable medication conveyance system [71, 72]. It is an exceptional carrier material for the local and controlled medication conveyance system [73]. Many kinds of polymers for example poly (lactide-co-glycolide) (PLG) are utilized to accomplish the maintained arrival of proteins and peptide [74]. It offers numerous benefits, for example, their biodegradability, beautification and portrayal, simple blend and high biocompatibility [75]. In natural and restorative fields hydrogel play an extraordinary role [76]. The supramolecular hydrogels containing peptides assume a job to create a prescription, as they make novelty in regions traversing from new helpful for example coordinate cell fate [77, 78]. Surgical methodology improved the immune response of vaccines [79].

Tissue regeneration and tissue engineering

The term "tissue engineering" was initially characterized in 1988 as the "use of the standards and techniques for building and life sciences toward principal knowledge of structure-work relationship in typical and obsessive mammalian tissues and the arrangement of natural substitutes for the repair or recovery of tissue or organ function" [80]. Tissue building is a present use of hydrogels in which they can be connected as space-filling specialists as conveyance vehicles for bioactive substances or as three-dimensional structures that sort out cells and present boosts to guarantee the improvement of a required tissue. Hydrogels have a small scale designs like that of common extracellular matrix (ECM), subsequently these have been used to help re-design of the scope of tissues for example bones, ligament, nerves, vessels and skin [81]. Poly (ethylene glycol) has more biocompatibility, absence of poisonous impacts on the encompassing tissues and high dissolvability in water which fills in as great possibility for medication conveyance systems [82]. They are used for cell conveyance to enhance tissue recovery. Hydrogels that are set up from silk strands arranged magnificent interstitial liquid help limit and they are utilized for specific ligament restore [83]. Poly (urethane) hydrogels fill in as medication lattices, artificial

kidney films and catheter covering materials [84]. In tissue designing alginate can be utilized as an immune isolation hindrance [85]. Dextran is regular polysaccharide which are utilized in tissue building the most intriguing normal for dextran are its protein dismissal properties, the alleged non-fouling, [86] combined with incredible biocompatibility because of its glycocalyx mimic behavior [87]. This feature is valuable to make an extracellular fluid-like hydrogel for tissue building. Hydrogel platforms have likewise been connected to transplant cells and to build numerous tissues in the body including ligament, bone and smooth muscle [88].

Drug delivery in the oral cavity

A large portion of the mouth ailments, for example, periodontal malady, viral contaminations, stomatitis and oral depression growths are treated by locally tranquilize conveyance framework. Medication containing hydrogel having the capacity to follow against the salivary stream for a more drawn out term, which washes the oral cavity mucosa, is requisite to accomplish this nearby medication conveyance. Hydrogels offer a decent potential as oral helpful frameworks because of biocompatibility, assorted variety of both common and engineered material alternatives and tunable characteristics [89]. Stimuli-responsive hydrogels are specifically interested for oral conveyance as they can react to ecological changes to adjust organize structure, swelling conduct, penetrability or mechanical quality and can control sedate release [90]. Many different physical and chemical upgrades have been connected to smart hydrogel frameworks. Physical upgrades incorporate temperature, electric field, light and solvent composition. Chemical and biochemical improvements for example pH, ionic quality and sub-atomic acknowledgment occasions, are all the more usually abused in oral delivery [91]. Oral conveyance is attractive for a decent variety of therapeutics for the treatment of both systematic and local diseases. However, many drugs are not feasibly delivered in the same method as conventional small-molecule drugs. For example, protein and peptide drugs suffer poor stability in the GI tract, being liable to enzymatic debasement, acidic denaturation, low solvency and absorption [92]. Hydrogels are appropriate for the oral conveyance of little, hydrophilic atoms and macromolecular medications (~ 400 Da to 30 kDa) [93].

Ophthalmic

Liquid ophthalmic systems generally indicate short bioavailability due to steady lachrymation and quick nasolacrimal drainage [94, 95]. Subsequently, short dosing interval and high medication fixations are expected to achieve viable remedial levels this may consequence in non-adherence of patients [96]. Corrective soft contact lens (SCL) is without uncertainty the most widely recognized and best commercial use of hydrogels. Another field of movement is the advancement of new polymers with antifouling characteristics to decrease the adsorption of proteins and cells on the lens surface [97]. This may enhance the biocompatibility of soft contact lens, particularly amid long term wear. The second significant advancement has been the improvement of based lens materials. These silicone hydrogels consolidate them to a great degree high oxygen porousness of poly (dimethylsiloxane) and the wearing comfort of regular poly (2-hydroxyethyl methacrylate) (pHEMA) hydrogels. Among all boosts responsive frameworks, hydrogels delicate to the ionic quality are most across the board and have ended up being best. Watery arrangements of specific polymers, for example, gellan gum (gelrite) or alginate, frame hydrogels after installation into the conjunctival sac through the nearness of cations in the tear liquid. Gellan gum is a direct, anionic heteropolysaccharide comprising of glucose, glucuronic acid and rhamnose [98]. An answer of 0.6% gellan gum was shown to improve the precorneal residence time and, subsequently, the bioavailability of timolol [99]. PVA-based hydrogels are utilized generally in artificial tears, contact lenses [100]. Due to their versatile properties, hydrogels can represent an ocular drainage resistant gadget. What's more, they may offer better inclination with to a lesser degree a coarse sensation to patients.

Cancer treatment

Drug delivery systems possess drug carrier hydrogels [101] that bear the bioactive antineoplastic agent inside the scaffold. The

development of hydrogels mainly depends on natural and synthetic polymers as the drug carriers needed special attention. These biomaterials present an exciting opportunity for designing new methods of cancer therapy [102]. Hydrogel-based drug delivery system have been appeared to enhance chemotherapy results and gene therapy adequacy by expanding drug half-life, encouraging controlled and customizable medication discharge and in this way diminishing non-targeted presentation. Hydrogels grant scientists an extensive variety of conceivable outcomes to improve disease drug delivery system [103, 104]. Likewise, broad research has been accomplished on malignancy imaging changeless tissue substitution and brief prosthesis regions in which hydrogels play key roles [105, 106]. Polyethylene glycol Hydrogel is a water-dissolvable and biocompatible polymer and is the most widely recognized nonionic medication freight for malignancy drug delivery system. Additionally, it is the most pertinent unit for polypeptide alteration [107]. Thermoresponsive hydrogels have been reported as delivery systems for chemotherapeutic agents because they can be injected as a liquid into the tumor and then gelled at body temperature. OncoGel TM is an example of an anticancer drug-loaded thermoresponsive hydrogel [108].

Cosmetic

The corrective business is on the development of hydrogels positively a pH-sensitive material P(MAA-co-EGMA) has been formulated for the arrival of beautifiers medications for example arbutin, adenosine and niacinamide, well-known particles for maturing treatment and for skin-whitening [109]. pH sensitive hydrogels change is penetrability reacting to the pH changes, the porousness rises as the gel interacts with skin (pH-6) and this conduct is because of the ionization/deionization of MAA carboxylic gatherings. Thermosensitive hydrogel plans are used in healthy skin and skin treatment as transdermal conveyance frameworks. Hyaluronic acid has been generally utilized as an enemy of maturing restorative fixing both topically and orally. In temperature-delicate state-evolving hydrogel when its scope to contact with our skin and achieves the body temperature, consistently and rapidly discharges the dynamic fixing into the skin. Also is utilized as a vehicle for topical use of medications to the skin. It has been exhibited in the truth that hyaluronic acid is ingested from the surface of the skin and goes quickly through the epidermis [110].

Agriculture

Hydrogels are also used in agriculture. It plays an indispensable capacity in agriculture. A majority of hydrogels marketed formulation for agriculture gained from crosslinked acrylamide-acrylate copolymers, polyacrylamides and as they remain active for a much longer time. Hydrogels are created to raise the physical properties of soil for example to improve the water holding limit of soil and soil porousness and invasion rates. To enhance the growth of plants and performance hydrogels can be used to reduce water stress. Cross-connected polyacrylamide hydrogels are considered as potential transporters for insecticides, fungicides and herbicides [111].

Hair loss

Hair loss is a common ailment and can be stressful for the people experiencing it. Genes, illness, trauma and surgery are a number of factors can lead to temporary or permanent hair loss. However, alopecia is a hair growth problem which is caused due to abnormal growth cycle or reduction in the size of hair follicles. The researcher group which included from the ITC life sciences and technology center in bangalore developed the hydrogel by combining a mixture of silk proteins, isolated from silkworm cocoons and gelatin. Tyrosinase enzyme was used to develop a stable hydrogel system [112].

CONCLUSION

Significant advancement has been made in the field of hydrogels as a utilitarian biomaterial. Hydrogels accomplish a controlled discharged of proteins and peptides because of their ability to consolidate dynamic fixing into the hydrophilic polymer organize the structure. The delicate nature, permeable structure and extensive water content make hydrogels appropriate transporters to consolidate a considerable measure of medications and to give

managed discharge to a predetermined timeframe. Their qualities empower them to be utilized as basic apparatuses in all fields, for example, biomedical, horticultural, mechanical and natural territories. We additionally expect expanded learning of the piece of hydrogel material will permit controlling the arrival of more delicate medications. The hydrogel can be created from nano-sized particles named as nanohydrogel, or, in other words, give enhanced steadiness to biopharmaceuticals, for example, peptides and proteins. Wound contaminations are significant difficulties in the injury care administration. Infection can be either due to microbial attack or due to some diseases. The majority of current wound dressing materials lack the property of adequate exudates absorption and many of them may adhere to wound which can cause trauma. Most of the dressing materials are non-biodegradable and need regular replacement. A myriad of dressings does not possess antibacterial activity as well as hemostatic potential. Lack of

flexibility, mechanical strength, and wet strength are other demerits of existing dressing materials. Current dressing materials are not ready to keep up a damp domain at the injury/dressing interface. Hydrogel-based wound dressings with antimicrobial activity can be used to tackle such situations. Hydrogels based dressings provide a soothing effect to the wound, allows the transfer of oxygen and acts as a barrier against microbes. Our prepared composite bandages were microporous and flexible in nature. The prepared hydrogel based composite dressing materials were capable of providing sustained antimicrobial activity and excellent blood clotting potential. The prepared bandages can be utilized as a medication conveyance framework for different illnesses like osteoporosis, skin tumor and so forth utilizing this strategy, controlled medication discharge and discharge at the correct area can be accomplished. Now today new invention hydrogel is used in the treatment of alopecia.

Table 1: Hydrogel-based formulation which is approved by the regulatory agency FDA [113]

S. No.	Product	Drug	Regulatory status	Use
1.	Atridox	8.5%Doxycycline	approved by FDA	periodontal treatment product with Sub-gingival Delivery
2.	Eligard	Leuprorelin acetate	approved by FDA	for the treatment of prostate cancer
3.	Lupron Depot	Leuprorelinacetate	approved by FDA	treatment of prostate cancer
4.	Sandostatin	Octreotide acetate	approved by FDA	Acromegaly
5.	Cervidil	Dinoprostone	approved by FDA	continuation of cervical ripening or near term
6.	Timoptic-XE	Timolol maleate	approved by FDA	Glaucoma

Table 2: List of patents on hydrogel drug delivery system

S. No.	Publication year	Patent number/publication number	Title	Inventor	Reference
1.	2017	US20170239359A1	Anhydrous hydrogel composition and delivery system	John Borja	[114]
2.	2017	20170304489	Time controlled glucose releasing hydrogels and application thereof	Mickael Deschepper	[115]
3.	2017	US 9,700,635 B2	Hydrogels from dynamic covalent networks	Dylan J. Boddy, Tucson, AZ (US); Mareva B. Fevre, San Jose, CA (US);	[116]
4.	2016	US9,254,267B2	Composite hydrogel drug delivery systems	Amarpreet S. Sawhney	[117]
5.	2014	US 8,658,147 B2	Polymer hydrogels and methods of preparation thereof	Alessandro Sannino, Lecce (IT)	[118]
6.	2014	US20140065226A1	Thermo-responsive hydrogel compositions	Eric Brey	[119]
7.	2013	US2013/0018110A1	Hydrogel synthesis	Vitaliy Khutoryanskiy	[120]
8.	2012	US20120238644A1	Fragmented hydrogel	Glen gong	[121]
9.	2012	US20120100103 A1	In situ forming hydrogel and biomedical use thereof	Ki dong park	[122]
9.	2011	WO2011111067 B2	A biodegradable polymeric hydrogel system	Hemant Ravindran	[123]

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

Declared none

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